UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,909	10/29/2003	James B. Lorens	021044-005820US	9257

20350 7590 05/07/2007

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
REDDIG, PETER J	
ART UNIT	**PAPER NUMBER**
1642	

MAIL DATE	DELIVERY MODE
05/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/696,909	LORENS ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-12,14-19 and 54* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-12,14-19 and 54 (as drawn to the method of claim 1, species in vitro assay)* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/01/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 27 and 40-44 54 (as drawn to the method of claim 27) .

DETAILED ACTION

1. The Amendment filed February 23, 2007, in response to the Office Action of August 23, 2007 is acknowledged and has been entered. Previously pending claims 3, 13, 28-39 and 45-53 have been cancelled and claims 1, 19, 27 and 54 have been amended.

2. Claims 27, 40-44 and 54 (as drawn to the method of claim 27) have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions per Applicant's election of *in vitro* as the location for identification of a compound that modulates angiogenesis in the remarks of July 12, 2006 and the claims as currently constituted are drawn to an *in vivo* method.

3. Claims 1, 2, 4-12, 14-19 and 54 (as drawn to the method of claim 1, species in vitro assay) are currently being examined.

4. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 2, 4-12, 14-19 and 54 remain rejected under 35 U.S.C. 112 for the reasons previously set forth in the Office Action of August 23, 2006, section 8, p. 4-10.

Applicant argues that factors such as the amount of guidance presented in the specification and the presence of working examples must be considered to determine whether undue experimentation is required to practice the claimed invention. See, e.g., Ex Parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1985) and in re Wands', 8 USPQ2d 1400 (Fed. Cir. 1988). As described in Wands', "a considerable amount of experimentation is permissible, if it is merely

routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Wands', USPQ2d at 1404, quoting In re Jackson, 217 USPQ 804 (Bd. Pat. App. & Int. 1982). Applicant argues that moreover, "[a] patent need not teach, and preferably omits, what is well known in the art." MPEP 2164.01 citing In re Buchner, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. MonoclonalAntibodies, Inc., 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 221 USPQ 481,489 (Fed. Cir. 1984). V. American Hoist & Derrick Co., 221 USPQ 481,489 (Fed. Cir. 1984). Applicant argues that as set forth in the Manual of Patent Examining Procedure (MPEP) § 2164.01, "the test of enablement is not whether any experimentation is necessary, but whether.., it is undue." Applicant argues that further, the "fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" (citations omitted). Applicant argues that finally, claims reading on inoperative embodiments are enabled if the skilled artisan understands how to avoid inoperative embodiments. See, e.g., In re Cook and Merigold, 169 USPQ 299, 301 (C.C.P.A. 1971).

Applicant argues that the amended claims are directed to methods of identifying inhibitors of angiogenesis using Axl proteins with 95% identity to the full length of SEQ ID NO: 4, wherein down regulation of the Axl protein results in inhibition of angiogenesis. Applicant argues that the specification provides support for the amended claims by providing SEQ ID NO: 4, sequence analysis algorithms to identify proteins with 95% identity to SEQ ID NO: 4. Additionally, Applicant argues that the fact that Axl was known to be a tyrosine kinase at the

time of filing and Ax1 kinase assays can be used to easily identify Axl polypeptides provides support for the enablement of the claims, see page 8, para 3.

It is noted that Applicant states that the amended claims are directed to methods of identifying inhibitors of angiogenesis using Axl protein with 95% identity to the full length of SEQ ID NO: 4, wherein down regulation of the Axl protein results in inhibition of angiogenesis at page 8 of the instant response. However, it is noted that Applicant's interpretation of the claims does not reflect the claims as currently constituted as no limitation drawn to down regulation of Ax1 protein is found in the claims.

The argument has been considered, but has not been found persuasive because although claim 1 recites that the claimed 95% polypeptide has kinase activity, there is no limitation in the claim that suggests that the "functional effect" required for identifying a compound that inhibits angiogenesis is in any way associated with the kinase activity of the polypeptide. Thus, even if one were to be able to predictably identify an Axl polypeptide with greater than 95% identity to full length SEQ ID NO: 4 that had kinase activity, this function is not required to be either necessary or sufficient to identify the compound that inhibits angiogenesis and thus appears to be irrelevant to the claimed invention and for the reasons previously set forth as drawn to the teachings of Bowie et al., Burgess et al., and Lazar et al. which demonstrate the unpredictability of predicting protein function from sequence data, one of skill in the art could not predictably determine which of the less than 5% of the amino acids of SEQ ID NO: 4 could be altered so that the invention would function as claimed.

Applicant argues that in two recent decisions by the Board of Patent Appeals and Interferences, Ex parte Sun, Appeal No. 2003-1993 and Ex parte Bandman, Appeal No. 2004-

2319, the board found that claims directed to sequences with 80% or 95% identity to a reference sequence were enabled because the supporting specifications provided a single reference sequence and an assay for activity of the encoded protein. Applicant argues that as discussed above, the specification and knowledge in the art provide the Axl amino acid sequence and kinase assays for the recited Axl activity. Applicant argues that thus, based on these recent Board decisions, the claims are enabled.

The argument has been considered, but has not been found persuasive because, even if the function of kinase activity of the claimed Axl polypeptide were either necessary or sufficient for the identification of the compound that inhibits angiogenesis a review of the Board decisions drawn to *Ex parte Bandman* and *Ex Parte Sun* reveal that the fact patterns of those two cases are very different from the fact pattern found in the instant case.

In particular, a review of *Ex parte Bandman* reveals that although the Board did decide that the recitation of a single sequence met the Written Description Guidelines for the genus of the polypeptides claimed, unlike the instantly claimed **Axl protein** (emphasis added) having 95% identity to SEQ ID NO: 4, the claimed invention of *Ex parte Bandman* was drawn to **naturally occurring amino acid sequences** (emphasis added) that are at least 95% identical to a wild-type sequence. The court found that "through the process of natural selection, nature will have determined the appropriate amino acid sequences". In the instant application the claim is clearly NOT LIMITED to "naturally occurring" amino acid sequences" and thus nature will not have determined the appropriate amino acid sequences.

In particular, a review of *Ex Parte Sun* reveals that although the Board did decide that the recitation of a single sequence met the Written Description Guidelines for the genus of

polypeptides claimed, this decision was based not only on the disclosure of the specific chemical structure of a polynucleotide comprising the coding sequence set forth in SEQ ID NO: 1, and the teaching on how to test for wee1 activity but also the teaching of the areas of the wee1 gene that can be altered without disturbing substrate recognition. The Board states that "What is evident from the record is those of ordinary skill in the art were aware that most of the variations in amino acid sequences of WEE1 are in the amino terminus, while the carboxy end of the genes are relatively conserved. Those of skill in the art were also aware that the carboxyl terminus and the central portion of the WEE1 protein ..... contain the protein kinase domains and sequence crucial for substrate recognition and catalysis. Thus, those of ordinary skill in the art would have recognized from reading the disclosure that the inventors had invented the isolated wee1 having the specific nucleotide and amino acid sequences and variations of these sequences with mutations in described specific areas of Wee1, while avoiding the introduction of mutations in other regions. This teaching, coupled with the ability to test for functional mutants with the assays provided for in the specification, supports Applicant's position." However, unlike the fact pattern in *Ex Parte Sun*, the only assay argued is the kinase assay, wherein the claims are not drawn to inhibition of kinase activity, thus the instant fact pattern does not provide an assay for testing the claimed, but undefined functional effect.

Thus, contrary to Applicant's arguments, the fact pattern of the instant case is not consistent with the fact pattern of the cited Board decisions wherein the claims that were subject to the decisions were supported by disclosure of a single reference sequence.

Applicant's arguments have been considered, but have not been found persuasive and the rejection is maintained.

6. Claims 1, 2, 4-12, 14-19 and 54 remain rejected under 35 U.S.C. 112 as lacking an adequate written description for the reasons previously set forth in the Office Action of August 23, 2006, section 12, p. 21-24.

Applicant argues that the specification does provide descriptive support for the full scope of the claimed invention by providing both SEQ ID NO: 4, a reference sequence for the recited polypeptides, and assays for regulation and inhibition of angiogenesis. Applicant argues that Axl kinase activity was well-known at the time of filing. Applicant argues that the assays are described throughout the specification, for example, regulation and modulation of angiogenesis and tumorigenesis. Applicant argues that this information is more than adequate to meet the written description requirement, particularly in view of Enzo, cited above, recent Board decisions, and the interpretation of the Written Description Guidelines evidenced by the USPTO's own Synopsis of Application of Written Description Guidelines.

The argument has been considered but has not been found persuasive because although the claim states that the polypeptide has kinase activity, this activity is not required to be either necessary or sufficient for determining the functional effect of the compound upon angiogenesis and since no specific function is required to be effected, no nexus can be found between structure and function and the written description requirements are not met.

Applicant argues that in the Sun and Bandman decisions by the Board of Patent Appeals and Interferences, the board found that claims directed to sequences with 80% or 95% identity to a reference sequence were described because the supporting specifications provided a single reference sequence, teachings of areas of the claimed sequences that could be modified, and a

functional assay for activity of the encoded proteins. Applicant argues that such teachings are included in the present application, as indicated above.

Applicant points to Example 14 of the Synopsis of Application of Written Description Guidelines, which analyzes a claim directed to a protein with an amino acid sequence at least 95% identical to SEQ ID NO: 3 and that has a catalytic activity. Applicant argues that in Example 14, the specification provided one example of a protein that was a member of the claimed genus. Applicant argues that The Patent Office concluded that the claim of 95% identity to a reference sequence with a specified catalytic activity was adequately described within the meaning of 35 U.S.C. § 112, first paragraph. Applicant argues that the Synopsis reasons that the genus of proteins that must be variants of the claimed SEQ ID NO: 3 does not have substantial variation since all of the members must have 95% identity to the reference sequence and must have the specified catalytic activity. Applicant argues that therefore, according to the Synopsis, the "single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay... "that could be used to identify members of the claimed genus. Applicant argues that As described above, the specification discloses the angiogenesis activity of the recited Axl proteins and assays for its measurement. Thus, at a minimum, on the basis of the Synopsis of Application of Written Description Guidelines issued by the USPTO, the present claims that recite 95% identity to SEQ ID NO: 4 meet the written description requirement.

The arguments have been considered but has not been found persuasive because for the reasons set forth above, the description drawn to kinase activity does not appear to be relevant to the claimed invention because although the claim states that the polypeptide has kinase activity,

this activity is not required to be either necessary or sufficient for determining the functional effect of the compound upon angiogenesis and since no specific function is required to be effected, no nexus can be found between structure and function and the written description requirements are not met. Thus, the teachings of Example 14 are also not relevant.

Again, a review of the Board decisions drawn to *Ex parte Bandman* and *Ex Parte Sun* reveal that the fact patterns of those two cases are very different from the fact pattern found in the instant case.

In particular, a review of *Ex parte Bandman* reveals that although the Board did decide that the recitation of a single sequence met the Written Description Guidelines for the genus of the polypeptides claimed, unlike the instantly claimed **Axl polypeptide** (emphasis added) having 95% identity to SEQ ID NO: 4, the claimed invention of *Ex parte Bandman* was drawn to **naturally occurring amino acid sequences** (emphasis added) that are at least 95% identical to a wild-type sequence. The court found that "through the process of natural selection, nature will have determined the appropriate amino acid sequences". In the instant application the claim is clearly drawn to recombinant polypeptide, it is not drawn to "naturally occurring" amino acid sequences" and thus nature will not have determined the appropriate amino acid sequences.

In particular, a review of *Ex Parte Sun* reveals that although the Board did decide that the recitation of a single sequence met the Written Description Guidelines for the genus of polypeptides claimed, this decision was based not only on the disclosure of the specific chemical structure of a polynucleotide comprising the coding sequence set forth in SEQ ID NO: 1, and the teaching on how to test for wee1 activity but also the teaching of the areas of the wee1 gene that can be altered without disturbing substrate recognition. The Board states that "What is evident

from the record is those of ordinary skill in the art were aware that most of the variations in amino acid sequences of WEE1 are in the amino terminus, while the carboxy end of the genes are relatively conserved. Those of skill in the art were also aware that the carboxyl terminus and the central portion of the WEE1 protein ..... contain the protein kinase domains and sequence crucial for substrate recognition and catalysis. Thus, those of ordinary skill in the art would have recognized from reading the disclosure that the inventors had invented the isolated wee1 having the specific nucleotide and amino acid sequences and variations of these sequences with mutations in described specific areas of Wee1, while avoiding the introduction of mutations in other regions. This teaching, coupled with the ability to test for functional mutants with the assays provided for in the specification, supports applicant position." However, unlike the fact pattern in *Ex Parte Sun*, the instant fact pattern does not provide an assay for testing the claimed function of the instant invention, does not provide information drawn to a correlation between the structure and function of the claimed polypeptide.

Thus, contrary to Applicant's arguments, the fact pattern of the instant case is not consistent with the fact pattern of the cited Board decisions wherein the genus claims that were subject to the decisions were supported by disclosure of a single representative species.

Applicant's arguments have not been found persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 2, 5, 6, 9-11, 14, 19, and 54 remain rejected under 35 USC 102 for the reasons previously set forth in the Office Action of August 23, 2006, section 13, p. 24-27.

Applicant argues that to anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found...in a single prior art reference." Verdegaal Bros. v. Union Oil of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicant argues that thus, in order to anticipate, the cited reference must contain every element of the claims at issue. Applicant argues that as amended, independent claim 1 is directed to a method of identifying a compound that inhibits angiogenesis, by contacting the compound with an Axl polypeptide, and determining the functional effect of the compound upon the Axl polypeptide to identify the compound that inhibits angiogenesis. Applicant argues that Healey et al. does not demonstrate that Gas-6 inhibits angiogenesis in the HPAEC that comprise the Axl protein. Applicant argues that Healey et al. disclose that the antiapoptotic activities of Gas-6 are "relevant to endothelial cell survival in the quiescent environment of the vessel wall." See, e.g., Healey et al. abstract at page L 1273. Applicant argues that, thus, Gas-6 activation of the Axl protein is used to promote endothelial cell survival when angiogenesis is not occurring. Applicant argues that , therefore, Healey et al. does not disclose identification of an inhibitor of angiogenesis using the Axl polypeptide and cannot anticipate the claims.

Applicant's arguments have been carefully considered, but have not been found persuasive and the rejection is maintained.

Although Healy does not teach that Gas-6 specifically inhibits angiogenesis but only states that Gas-6 is relevant to endothelial cell survival in the quiescent environment of the cell wall and measures the apoptotic effect of Gas6/Axl on endothelial cells, given that the method does not define the functional effect, given that incubation with Gas6 has a functional effect on

Axl the prior art reference meets the limitations of the claims because, the method of the prior art comprises the same method steps as claimed in the instant invention, that is, the method comprising the steps of: (i) contacting the compound with an angiogenesis polypeptide comprising an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 95 % identity to full length SEO ID NO: 4 and wherein the angiogenesis polypeptide has kinase activity; and (ii) determining the functional effect of the compound upon the angiogenesis polypeptide. Given that, as evidenced by Galliccio et al. (Blood, 1 March 2005, Vol. 105, No. 5, pp. 1970-1976) (see Abstract), the interaction of Gas-6 with Ax1 inhibits VEGF-dependent angiogenesis, it is clear that the claimed method is anticipated because the method will inherently lead to identifying compounds that inhibit angiogenesis. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Thus, Applicant's arguments have not been found persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 12 and 15-18 remain rejected under 35 USC 103 for the reasons previously set forth in the Office Action of August 23, 2006, section 17, p. 35-36.

Applicant argues that Claims 12 and 15-18 depend from claim 1, and the Office Action applies the analysis discussed above to Healey et al. Applicant argues that the Office Action

asserts that Varner and Cherish disclose that integrin αVβ3 is significantly upregulated on vascular cells and plays a biological role in blood vessel formation and that Panzer et al. and Ruoslahti et al. teach general method of screening compounds for a desired effect.
Applicant argues that Healey et al. teaches away from use of the Axl polypeptide to identify compounds that inhibit angiogenesis. Applicants assert that Healey et al. teaches that Axl and its ligand Gas-6 have anti-apoptotic activity in the tested human pulmonary artery endothelial cells (HPAEC).

Applicant argues that Healey et al. disclose that the antiapoptotic activities of Gas-6 are "relevant to endothelial cell survival in the quiescent environment of the vessel wall." See, e.g., Healey et al. abstract at page L1273. Applicant argues that thus, according to Healey et al. Gas-6 activation of the Axl protein is used to promote endothelial cell survival when angiogenesis is not occurring. Applicant argues that therefore, Healey et al. does not teach or suggest use of the Axl polypeptide to identify compounds that inhibit angiogenesis.

Applicant argues that the Office Action alleges that Varner and Cherish disclose a role for integrin αVβ3 in angiogenesis. Applicant argues that however, Varner and Cherish do not teach or suggest a role for Axl in angiogenesis and, therefore, cannot be used to cure the deficiencies of Healey et al. Applicant argues that the other cited references, Panzer et al., and Ruoslahti et al. disclose only general methods of screening small molecules and other compounds for a desired effect. Applicant argues that no discussion of the Axl polypeptide or a role in angiogenesis is disclosed. Applicant argues that Panzer et al., and Ruoslahti et al. cannot be used to cure the deficiencies of Healey et al. Applicant argues that thus, alone or in combination, the cited references cannot be used to provide a prima facie case of obviousness.

Applicant the argument has been carefully considered but not found persuasive because Applicant has argued and discussed the references individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references, which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413,208 USPQ 871 (CCPA 1981).

For the reasons previously set forth in the Office Action of August 23, 2006, section 17, p. 35-36, one would have been motivated to perform the method of claim 1 by measuring $\alpha V\beta 3$ expression and to use an antibody, antisense molecule, RNAi, or small organic molecule as the compound to use in the screening method because the level $\alpha V\beta 3$ expression was known to be important in angiogenesis and the screening of various inhibitory compounds for therapeutic purposes was conventionally used in the art at the time of the invention. Thus one of ordinary skill in the art would have had motivation and a reasonable expectation of success in making and using the claimed invention.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. If Applicant were able to overcome the rejections set forth above under 35 U.S.C. 112, first paragraph, claims 1, 2, 4-12, 14-19 and 54 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a compound that inhibits angiogenesis, the method comprising the steps of: (i) contacting the compound with an angiogenesis polypeptide comprising an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 95% identity to full length SEQ ID NO: 4 and wherein the angiogenesis polypeptide has kinase activity; and (ii) determining **if the compound downregulates the angiogenesis polypeptide**, thereby identifying the compound that inhibits angiogenesis, does not reasonably provide enablement for a method for identifying a compound that inhibits angiogenesis, the method comprising the steps of: (i) contacting the compound with an angiogenesis polypeptide comprising an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 95% identity to full length SEQ ID NO:4 and wherein the angiogenesis polypeptide has kinase activity; and (ii) determining the **functional effect** of the compound upon the angiogenesis polypeptide, thereby identifying the compound that inhibits angiogenesis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a method for identifying a compound that inhibits angiogenesis, the method comprising the steps of: (i) contacting the compound with an angiogenesis polypeptide comprising an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 95% identity to full length SEQ ID NO: 4 and wherein the angiogenesis polypeptide has kinase activity; and (ii) determining the functional effect of the compound upon the angiogenesis polypeptide, thereby identifying the compound that inhibits angiogenesis.

This means that determining **any** functional effect of the compound on the angiogenesis polypeptide will identify a compound that inhibits angiogenesis.

The specification teaches that RNAi to Axl reduces Axl protein levels, inhibits haptotaxis, inhibits proliferation, and inhibits endothelial tube formation in primary human endothelial cells (HUVEC), see Figures 11-15 and 17.

Furthermore, Applicant notes in the Remarks of 2/23/07 (p. 8, 3rd para.) that "The amended claims are directed to methods of identifying inhibitors of angiogenesis using Axl proteins with 95% identity to the full length of SEQ ID NO: 4, wherein **down regulation of the Axl protein results in inhibition of angiogenesis** (emphasis added). The specification provides ample support for these claims."

The specification teaches that the phrase "functional effects" in the context of assays for testing compounds that modulate activity of an angiogenesis and tumorigenesis protein includes

the determination of a parameter that is indirectly or directly under the influence of an angiogenesis polypeptide, e.g., a chemical or phenotypic effect such as loss-of angiogenesis or tumorigenesis phenotype represented by a change in expression of a cell surface marker $\alpha V\beta 3$ integrin, changes in cellular migration, changes in endothelial tube formation, and changes in tumor growth, or changes in cellular proliferation, especially endothelial cell proliferation; or enzymatic activity; or, e.g., a physical effect such as ligand binding or inhibition of ligand binding. A functional effect therefore includes ligand binding activity, the ability of cells to proliferate, expression in cells undergoing angiogenesis or tumorigenesis, and other characteristics of angiogenic and tumorigenic cells. "Functional effects" include in vitro, in vivo, and ex vivo activities, p. 8, lines 15-26. Additionally, it is noted that the specification teaches that "determining the functional effect" means assaying for a compound that increases or decreases a parameter that is indirectly or directly under the influence of an angiogenesis protein, e.g., measuring physical and chemical or phenotypic effects. Such functional effects can be measured by any means known to those skilled.

One cannot extrapolate the teachings of the specification to the scope of the claims because it is clear from the teachings of the specification and Applicants arguments that Applicant has only established a nexus between downregulation of Axl and inhibition of angiogenesis and not between angiogenesis and any of the other functional effects on Axl contemplated in the specification or claimed. Furthermore, it is well known in the identification of novel angiogenesis and cancer therapeutics (as is the clearly contemplated use for the claimed method, see p. 2, lines 5-22) is unpredictable.

In particular, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models that only 29 have actually been shown to be useful for chemotherapy (p. 1041, see 1st and 2nd para.). Furthermore, Kaiser (Science, 2006, 313, 1370) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para. Additionally, Clamp and Jayson (British Journal of Cancer, 2005 93:967-972) teach that the despite activity of the angiogenesis inhibitor endostatin in animal models, the clinical trial results were disappointing and only minor responses were observed (see Abstract and p. 969, left col.).

Given the unpredictability of the art of developing, given that no nexus has been established between any functional effect on Axl, except for downregulation of Axl, and given that the Applicant states that downregulation of Axl results in the inhibition of angiogenesis, one of skill in the art would could not predictably extrapolate the teachings of the specification to scope of the claims, where one can determine any functional effect on the angiogenesis polypeptide to identify a compound that inhibits angiogenesis.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention,

and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

10. All other objections and rejections recited in the Office Action of August 23, 2006 are withdrawn.

11. Applicant's amendment necessitated the new grounds of rejection. Thus, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

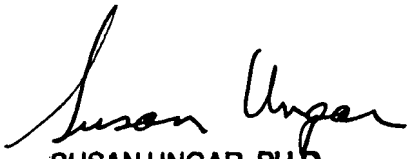
A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. ' 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

12. No claims allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0890. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642

PJR